



UNITED STATES PATENT AND TRADEMARK OFFICE

9
UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/681,753	10/09/2003	Christopher G. Williams	116567-023	8131

29180 7590 02/22/2007
BELL, BOYD, & LLOYD LLP
P.O. BOX 1135
CHICAGO, IL 60690

EXAMINER

SCHUBERG, LAURA J

ART UNIT	PAPER NUMBER
----------	--------------

1657

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/681,753

Applicant(s)

WILLIAMS ET AL.

Examiner

Laura Schuberg

Art Unit

1657

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 November 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 53-86 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 53-86 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 80, 82, 84-86 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 80, 82, 84-86 are ambiguous, and thus indefinite, because they are directed to both a composition and method (dependent upon claim 78), therefore it is not clear what Applicant is intending to claim: a composition or a method. See *Exparte Lyell*, 17 USPQ2d 1548 (Bd. Pat. App. & Inter. 1990) & MPEP 2173.05(p). While the claims are indefinite, in order to provide compact prosecution, the claims will be examined as composition claims and dependent upon claim 79.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States

only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 79 and 86 are rejected under 35 U.S.C. 102(b) as being anticipated by Dunn et al (Biotechnol. Prog. 1991).

Claim 79 is drawn to a multi-layered tissue construct fabricated *in vivo* comprising: a first layer comprising a first hydrogel; and a second layer comprising a second hydrogel, wherein the first layer is connected to the second layer and at least one of the first and second layers further comprises cells.

Claim 86 is drawn to the multi-layered tissue construct as recited in claim 79, wherein the first layer comprises a bioactive substance selected from the group consisting of: a nutrient, a cellular mediator, a growth factor, a compound which induces cellular differentiation, a bioactive polymer, a gene vector, or a pharmaceutical.
(Applicant elected growth factor)

Dunn teaches a method for culturing hepatocytes that includes adding a suspension of cells to an at least partially gelled first layer of collagen before adding a collagen solution on top of the first layer and then allowing the culture to gel and crosslink for attachment of the two layers before adding media (p.238 col1-2). In addition, media containing cells and growth factor are added to the first layer before the second layer is added (p.238).

Claim 79 is a product-by-process claim; claim 86 depends from said claim.
M.P.E.P. § 2113 reads, "Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps."

"Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." The structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product.

The use of 35 U.S.C. §§ 102 and 103 rejections for product-by-process claims has been approved by the courts. "[T]he lack of physical description in a product-by-process claim makes determination of the patentability of the claim more difficult, since in spite of the fact that the claim may recite only process limitations, it is the patentability of the product claimed and not of the recited process steps which must be established. We are therefore of the opinion that when the prior art discloses a product which reasonably appears to be either identical with or only slightly different than a product claimed in a product-by-process claim, a rejection based alternatively on either section 102 or section 103 of the statute is eminently fair and acceptable. As a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith."

Since Dunn explicitly teaches all the structural limitations of Applicant's claimed invention, Dunn therefore anticipates Applicant's invention as claimed.

Claims 79, 80, 86 are rejected under 35 U.S.C. 102(b) as being anticipated by Dionne et al (US 5,798,113).

Claim 80 includes wherein the first and second cells are different cell types.

Dionne teaches a dual-matrix vehicle which includes a suspension of pancreatic islet cells in an alginate solution, crosslinking the mixture with a CaCl_2 bath for a predetermined time, adding a second mixture of alginate to form a second layer and crosslinking again with a CaCl_2 bath (column 30 example 3). The CaCl_2 bath acts as a polymerization initiator. The addition of growth factors to the first layer is taught (column 9 line 55) as well as bioactive substances to the second layer (column 13 line 43-55). The addition of a second cell type encapsulated in the first hydrogel along with the first cell type is also taught (column 10 line 5-14).

Although the multi-layered tissue construct of Dionne is not fabricated *in vivo*, it does possess all the structural limitations as claimed by Applicant and therefore anticipates Applicant's invention as claimed for the same product-by-process reasons as described for the previous rejection.

Claims 79, 80, 82, 83, 86 are rejected under 35 U.S.C. 102(e) as being anticipated by Sah et al (US 2003/0077821 A1).

Claim 82 is drawn to the multi-layered tissue construct as recited in claim 79, wherein the first and second cells are the same cell type.

Claim 83 includes wherein the first cells and second cells are chondrocytes.

Sah teaches a tissue-engineered, cohesive cartilage construct comprised of two or more cartilage layers, wherein each cartilage layer comprises chondrogenic cells having a chondrocytic phenotype corresponding to superficial zone, middle zone, and deep zone chondrocytes (p.3 para 28). The polymerizable mixture taught by the reference is the cells and their associated matrix which form a hydrogel after a period of time in culture (p.9 para 82). Additional layers are not added until the current layer coalesces (p.9 para 82). Each layer of cells is taught to include the addition of growth factors (bioactive substances) (p.7 para 58) as well. The reference also teaches that the construct is not limited in the order of the layers of chondrocytes and that superficial zone chondrocytes can be adjacent to a layer containing deep zone chondrocytes (p.3 para 31). The order of layers found in natural cartilage is preferred and taught to be the first cells are deep zone chondrocytes, second cells are middle, and third cells are superficial (p.3 para 30). The first layer of the construct may also contain a second cellular type encapsulated in the first hydrogel (p.3 para 29).

Although the multi-layered tissue construct of Sah is not fabricated *in vivo*, it does possess all the structural limitations as claimed by Applicant and therefore anticipates Applicant's invention as claimed for the same product-by-process reasons as described for the previous rejection.

Claims 53, 61, 62, 63, 79, 80, 82, 83, 84 and 86 are rejected under 35 U.S.C. 102(e) as being anticipated by Mizuno et al (US 6,949,252 B2).

Claim 53 is drawn to a method of producing a multi-layered tissue construct *in vivo* comprising: providing a first polymerizable mixture; providing a second polymerizable mixture; wherein at least one of the first and second polymerizable mixtures comprises cells; placing a volume of the first mixture in the tissue space, then crosslinking the first mixture until forming an at least partially gelled first layer; and placing a volume of the second mixture in the tissue space, then crosslinking the second mixture until the second mixture is at least partially gelled to form a second layer. Dependent claims include polymerization initiators, the types of cells used, addition of bioactive substances, integration of the layers, exposure to external radiation, and additional forming of a third layer.

Mizuno teaches compositions and methods for preparing tissues and tissue constructs which include multi-layered systems comprising at least two layers (column 9 line 67). The process of placing polymer material in a lesion (*in vivo*) and, without waiting for it to fully polymerize, then placing neo-cartilage (chondrocyte seeded matrix) into position that is held in place by the first polymer, then applying a second polymer in a form that rapidly polymerizes (column 13 lines 40-50) is taught and shows *in vivo* production of a multi-layered tissue construct. This method anticipates Applicant's method as claimed.

Cells are present in at least one layer of the construct but may be also be present in three layers and may include three cell types (column 22 line 10- 32). The cellular layers are formed from a polymerizable mixture that forms a hydrogel by crosslinking (column 11 line 50- column 12 line 8). The addition of growth factors to the first and second layer is taught (column 10 line 5). The use of autologous cells is taught (column 25 lines 36-37) as well as chondrocytes (column 2 line 40).

Although some of the multi-layered tissue construct of Mizuno are not fabricated *in vivo*, they do possess all the structural limitations as claimed by Applicant and therefore anticipate Applicant's invention as claimed for the same product-by-process reasons as described for the previous rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

Art Unit: 1657

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 54-60, 64-78, 81, 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mizuno et al (US 6,949,252 B2) as applied to claims 53, 61, 62, 63, 79, 80, 82, 83, 84 and 86 above, and further in view of Langer et al (US 6,244,893 B1) and Anseth et al (Journal of Controlled Release 2002).

Claims 53 and 79 are drawn to the composition and method as described above.

Claim 66 is drawn to a method of producing a multi-layered tissue construct *in vivo* comprising: providing a first polymerizable mixture; providing a second polymerizable mixture; providing a third polymerizable mixture; wherein at least one of the first, second, and third polymerizable mixtures comprises cells; placing a volume of the first mixture in the tissue space, then crosslinking the first mixture until forming an at least partially gelled first layer; and placing a volume of the second mixture in the tissue space, then crosslinking the second mixture until the second mixture is at least partially gelled to form a second layer; repeating with the third mixture to form a third layer. Dependent claims include the types of cells used, addition of bioactive substances and the formation of the layers.

Mizuno teaches compositions and methods for preparing tissues and tissue constructs which include multi-layered systems comprising at least two layers (column 9 line 67). Cells are present in at least one layer of the construct but may be also be present in three layers and may include three cell types (column 22 line 10- 32). The

Art Unit: 1657

cellular layers are formed from a polymerizable mixture that forms a hydrogel by crosslinking (column 11 line 50- column 12 line 8). The addition of growth factors to the first and second layer is taught (column 10 line 5). The use of autologous cells is taught (column 25 lines 36-37) as well as chondrocytes (column 2 line 40). Mizuno teaches using ultraviolet radiation to crosslink the polymerizable mixture (column 12 line 6). The process of placing polymer material in a lesion and, without waiting for it to fully polymerize, then placing neo-cartilage (chondrocyte seeded matrix) into position that is held in place by the first polymer, then applying a second polymer in a form that rapidly polymerizes (column 13 lines 40-50) is taught and shows *in vivo* production.

Mizuno does not specifically teach producing the construct with a photoinitiator, mixing the polymer with second or third cells for *in vivo* formation of the construct or additionally crosslinking to form an integrated multi-layered matrix.

Langer teaches compositions for tissue engineering using photocrosslinkable polymeric hydrogels and photoinitiators with exposure to UV light for covalent crosslinking a polymer-cell suspension for formation of new tissue following injection (*in vivo* formation) (column 2). The polymer compositions can consist **solely** of covalently crosslinkable polymers in combination with an effective but non-toxic photoinitiator to allow for crosslinking using radiation provided by an external source and having cells suspended therein (column 3 line 44-line 50). Autologous cells are taught to be the most preferred (column 8 line 54). Chondrocytes and mesenchymal stem cells are taught to be used for the tissue construct as well (column 19 line 15-column 20 line 4).

Modifications and variations are intended for the described method (column 17 lines 20-25).

Anseth teaches medical applications benefit from the ability to fabricate polymers *in situ* such as adhesion of the polymer to surrounding tissue is generally significantly improved because of intimate contact of the polymer with the tissue during formation and the resulting mechanical interlocking that can arise from surface microroughness (page 200 column 1). Photoinitiated polymerizations overcome many limitations since the initiation does not require elevated temperatures, and the polymerization rate is sufficiently rapid, occurring over a short time period, which allows the system to overcome oxygen inhibition and moisture effects (page 200 column 1).

One of ordinary skill in the art would have been motivated to include a photopolymerizable polymer and a photoinitiator in the method of Mizuno because Langer and Anseth teach that they are suitable for polymerizing encapsulated cells. One of ordinary skill in the art would have had a reasonable expectation of success because Mizuno suggests the use of chemicals and radiation for solidifying the cellular support matrix (column 12).

One of ordinary skill in the art would have been motivated to mix the polymer with second or third cells for *in vivo* formation of the construct or additionally crosslinking to form an integrated multi-layered matrix because Anseth teaches the advantages of *in situ* (and inherently *in vivo*) formation of an engineered tissue construct. One of ordinary skill in the art would have had a reasonable expectation of success because Mizuno does teach at least one embodiment with *in vivo* formation of the tissue construct and all

the references are teaching methods using hydrogels for tissue engineering and photopolymerization.

Therefore, the combined teachings of Mizuno, Langer and Anseth render obvious Applicant's invention as claimed.

Response to Arguments

Applicant's arguments filed 11/29/2006 with respect to claims 53-86 have been considered but are moot in view of the new ground(s) of rejection. The arguments have been addressed in so far as they relate to the new rejections above.

Applicant argues that none of the prior art references disclose a multi-layered tissue construct formed in vivo or a method of producing the same. Applicant argues that the references only teach in vitro methods.

This is not found persuasive because with regard to the product-by-process claims, the structural limitations of the construct are present in the prior art references as described above. Since the patentability of a product does not depend on its method of production, the prior art anticipates all the patentable limitations as claimed by Applicant.

In addition, with regard to the method claims, the Mizuno and Langer references both disclose *in situ* applications that are performed on patients. *In situ* application and formation of a construct to a site in a patient constitutes an *in vivo* application and formation.

As for motivation to perform *in vivo* formation of a tissue construct, both Langer and Anseth provide specific motivation for performing *in vivo* formation as described in the rejections above.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

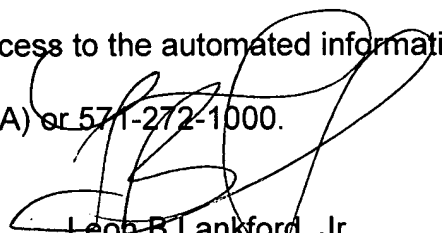
A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura Schuberg whose telephone number is 571-272-3347. The examiner can normally be reached on Mon-Fri 8:00-4:30.

Art Unit: 1657

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Leon B Lankford, Jr
Primary Examiner
Art Unit 1651

Laura Schuberg